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ADP013420

TITLE: Sources of Chemical Toxics and Their Precursors in
Pharmaceutical Industry

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This paper is part of the following report:

TITLE: Chemical and Biological Medical Treatment Symposium - Industry
II World Congress on Chemical and Biological Terrorism

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ADP013371 thru ADP013468

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50. SOURCES OF CHEMICAL TOXICS AND THEIR PRECURSORS IN PHARMACEUTICAL INDUSTRY

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Pharmaceutical industry includes a lot of independent units specialized in synthesis of active substances, their processing as pharmaceutical forms, control of intermediate and final products, storage of all these as well of a lot of adjuvants. In this long chain almost all manipulated chemical substances are biologically active, some of it very active and toxic. Consequently, the fact that Drug Companies represents a potential risk of chemical pollution is a common place. The fact that there were created a lot of laws and methods for avoiding this, is also clear. The present paper wants, starting from some accidents, which happened in spite of all preventing measures, to put in evidence some particular circumstances increasing the risk.

CLASSIFICATION OF SOURCES OF "TOXIC ACTION"

A first classification separates direct from secondary sources. This is important to keep in mind since, if for direct sources are provided a lot of safety measures, the secondary ones, appearing only in exceptional situations, are usually forgotten.

Direct sources: chemical raw materials (ingredients), synthesis intermediates, intermediate forms (solutions, powders), analytical reactivities, drugs itself, residues etc. Secondary sources are represented by chemical substances which derive from compounds mentioned as primary sources in exceptional cases following combustion and/or chemical interactions, chemical degradation etc.

Another point of view in classification arises from the type of discharge of toxic compounds. We have to consider separately the measures to counteract in:

- massive contamination and
- continuous, low doses contamination which can be considered also as a acute pollution.

Last but not least, starting from causes of contamination we can distinguish between

- "accepted", technological restrictions
- accidental sources,
- deliberated ("terrorist") actions.

Even in the case of accepted risks we have to separate between risks accepted by the companies but hidden to the people for surrounding area and unavoidable risks.

In function of the combination of different types of the above-mentioned characteristics we have different models in evaluation the spreading of toxic agent and its danger. Also different will be the measures for prevention and limitation of the effects.

SPECIFIC PROVISIONS IN PHARMACEUTICAL LEGISLATION FOR PREVENTING HAZARDS

Specific legislation for pharmaceutical activity are grouped in two never ending codes: Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP). Every accident or only perception of such possibility in pharmaceutical industry leads to new "articles" and even to new versions of these two fundamental "book of books".

GLP1 in preventing contamination

GLP include in a special chapter "Environmental risk assessment / ecotoxicity" a special

Note: Environmental risk for medicinal products where is written:

"Applications for marketing authorizations should include in Part IIIR an indication of any potential risks presented by the medicinal product for the environment. This requirement is particularly applicable to new active substances and live vaccines. Applications for new active substances may include in the documentation provided, an indication of relevant environmental hazards, making reference to standard physicochemical tests and any appropriate testing they have conducted on biodegradability, including some testing in sensitive species. Applications for live vaccines should consider issues such as shedding, survival and capacity to disseminate.

The pre-clinical Expert Report should include an evaluation of possible risks to the environment from the point of view of use and/or disposal and make proposals for labeling provisions which would reduce this risk."

GMP2 rules in preventing "errors" ask:

- "prevent contamination and mix-up: some of the substances used in modern medicines are very potent indeed, even in small trace amounts, and some people are more sensitive than others to very small traces"
- "guard against labeling or packaging errors".

As a remark, both GMP and GLP rules are very strict it concerns cleanliness, even paranoiac, in a similar manner with the rules for nuclear plants, but ignores rules for avoiding the infinitely greater risks associated with deliberated wrong actions.

CLASSIFICATION OF TERRORIST MANIPULATION OF TOXICS AND THEIR PRECURSORS

We have to take in consideration both non-specialist terrorists and specialist terrorist.

Further, specialization can concern terrorist actions or industrial pharmacy or, why not, both.

There is a significant difference between actions from outside of from inside the system.

Non-specialist scenario

The simplest idea is to orient the attack against chemical synthesis facilities from where a lot of volatile solvents could be spread in the atmosphere, resulting a contamination on large area. For example, to put fire exactly in the points were large panels warns on fire danger. The action is not easy to undertake since all this points are very well guarded and plans for limiting the disaster are usually disposable.

Specialist acting from inside the system: "pharmacist-terrorist", "chemist-terrorist".

This is not a common case but is by far the most "efficient" method for obtaining the maximum of damages, victims and terror. Almost all preventing measures and safety systems become worthless if exactly the man responsible for their application and management, blocks all mechanism. All systems, more or less sophisticated includes at least a man which know how is possible to block their run. The reasons for undertaking such suicidal actions are not impossible to find. The vengeance would be an example. But there are also other more foolish ideas. In pharmaceutical folklore the story goes about a proprietary of company producing fruit juices which put poison in a juice batch in order to determine, from the distribution of deceased people the places where are used his products. From that moment, for entering in the production area in pharmaceutical industry, is compulsory to change clothes and leave at the entrance all personal objects.

CONCRETE EXAMPLES

A massive release of ammonium from a tank following the deficiency of the tap appeared at the greatest Romanian drug company 20 years ago. The smudge covered and was felt on 1/3 of Bucharest. Almost all people in immediate neighborhood died following a holocaust of the respiratory tract. The accident was not reported by communist authorities but in medical scientific media was discussed much about the impossibility to find a treatment for such cases.

In Romania in the past decade cyanide ion appeared three times as chemical hazard.

First one concerned a "terrorist announcement" made at the national TV program in the first hours of Revolution, about the poisoning with cyanides of the greatest water pool from the south of country - the lake of Arges hydro-electric plant.

A tremendous contamination of the river Tisa with cyanides was produced after a sudden, great rain fall and the crushing of the dam of a basin with residues from a complex of mines from the north of Romania, in 2000.

A connection with the pharmacist-terrorist can be made if we remember that it was statistically established that pharmacists use for suicide cyanides, physicians use morphine and veterinarians - strychnine. Hence, the pharmacists believe that the most toxic substances are cyanides and a "pharmacist-terrorist" could use this substance for poisoning of a river or a water basin in a madness "revenge action". It seems that such an action would imply a great number of victims.

But, in the above mentioned accident it was observed that, in spite of the predictions of the specialists from Ministry of Environment, it was not produced a quick dissipation of the cyan and a "wave" of concentrated solution traveled for some two thousand kilometers on Tisa and Danube, until Black Sea.

This is compatible with a model of diffusion from a reservoir in an infinite medium if we consider a "mobile origin of coordinates in the point of contamination". In this conditions the convection term in the diffusion equation disappears and it obtains³ an analytic solution for the concentration c of polluting agent at the distance y from origin, at the moment t :

$$c(t,y) = c_0(1 - \operatorname{erf} \frac{y}{\sqrt{4Dt}}) \text{ where } \operatorname{erf}(x) = \frac{2}{\sqrt{\pi}} \int_{-\infty}^x e^{-\frac{\xi^2}{2}} d\xi$$

The conclusion is that, at least in the case of contamination of great rivers, the evolution of the risk can be predicted.

Another accident is very conclusive it concerns appearance of a lot of unexpected new conditions to favoring accidents. After a dishonest privatization a chemical laboratory entered into liquidation being shared to a lot of new owners. Some gypsy men had the idea to cut a reservoir with natrium cyanide and to sell it as scrap iron. The result was a massive pollution of the Siret river and a lot of victims following the consumption of fish from river. The situation is characteristic to transition period in eastern countries. A lot of chemical factories became almost "ownerless" or used in entirely different aims than their normal utilization.

CONCLUSIONS

1. Following the great number of utilized chemicals and products, there are a lot of possibilities for chemical contamination of environment in pharmaceutical industry.
2. GMP and GLP rules impose safety systems, apparently able to eliminate all possible risk.
3. A permanent risk remains from the most weak chain-loop of these systems: the man from inside the system, potentially a high-specialized chemist or pharmacist terrorist.

4. Sociopolitical events, which perturb both man and ownership relations are factors favoring unexpected and undesired evolutions of chemical and pharmaceutical sources.

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